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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
09/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/575,193	HATTORI ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *14,17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :4/12/07 2/11/08 5/29/08 1/8/09 6/26/09.

DETAILED ACTION

1. Applicant's response received June 23, 2009 is acknowledged.

Claims 1-19 are pending in the instant application.

Applicant's election without traverse of group I, claims 1-13, 15, 16, and 18, drawn to bispecific antibodies and kits and compositions comprising said antibodies in the reply filed on June 23, 2009 is acknowledged.

Claims 14, 17, and 19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 23, 2009.

Information Disclosure Statement

2. The IDS forms received 4/12/07, 2/11/08, 5/29/08, 1/8/09, and 6/26/09 are acknowledged and have been considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bispecific antibodies that bind factors IX and X and treat a bleeding disorder, does not reasonably provide enablement for generic bispecific antibodies that prevent bleeding disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed bispecific antibody products with the intended use

limitations of “treating” and “preventing” bleeding disorders, such as hemophilia A. The use of antibodies to blood coagulation factors such as factors IX and X to treat bleeding disorders is well known in the art as evidenced by US patents 6,005,091 and 7,033,590. However, the instant claims do not recite any antigen specificity, other than that the bispecific antibody binds "an enzyme" and "a substrate". It is not clear how such generic specificities are of use in treating specific disorders characterized by excessive bleeding, such as hemophilia A. Note that all of the working examples pertain to bispecific antibodies which bind factors IX and X.

Also, the instant specification does not appear to define “prevention”. As such, the broadest reasonable interpretation of the term is that 100% of bleeding is stopped in 100% of patients. Further, the instant specification does not appear to provide any working examples wherein products of the instant invention were administered to subjects (human or animal models) to determine in vivo efficacy. However, the working examples of the instant specification do indicate that the part of the bispecific antibody which binds factor IX is what comprises the factor VIII cofactor like activity, thus increasing the activity of factor IX to convert factor X to Xa. However, there are many bleeding disorders. One such disorder, hemophilia B, is characterized by a lack of factor IX activity, due either to mutations in the factor IX protein, the presence of inhibitors which bind factor IX, or both (Bolton-Maggs et al. The Lancet, 2003, 1801-1809, see entire document). Since the defect in such patients lies within factor IX, the products of the instant invention would be unable to "prevent" bleeding in such patients. Similarly, inhibitors to factor X also occur (Hsia et al., Am. J. Hematol. 1008, 83:318-320), and patients are known to comprise genetic deficiencies in factors V and X (Asselta et al. and Menegatti et al.). Indeed, excessive bleeding can occur in patients that have deficiencies in any or all of fibrinogen, prothrombin, FV, FVII, FX, FXI, FXIII, and von Willebrand factor (see particularly Table 2 of Bolton-Maggs) and thus it is not clear how the claimed antibodies can reduce bleeding in such patients, since many of these polypeptides are downstream of factor X in the coagulation cascade. With regard to hemophilia A, bispecific antibodies appear to work because they bypass the need for factor VIII to achieve coagulation. However, It is known that thrombin can be generated

by many pathways, some of which do not require FVIII (Price et al., Anaesthesia, 2004,59:483-492, see entire document, particularly Figures 1 and 2) and that coagulation can occur even in the presence of FVIII inhibitors (see also lines 31 and 32 of page 4 of the specification). Further, the claims read on the "prevention" of bleeding in a hemophilia A patient, and thus a reasonable interpretation of the claim is that said patent does not exhibit excessive bleeding when faced with an environmental insult, such as a laceration. To achieve this, the claimed products would need to be administered to the hemophilia A patient prior to said patient getting cut. However, hemophilia A patients do not deliberately cut themselves, so it is not predictable when they will be in need of increased coagulation efficacy. Note that the products of the working example continually promote factor X activation, and excessive levels of factor X activation can lead to unwanted thrombosis formation which could lead to diseases such as stroke and thus it does not appears reasonable that a hemophilia A patient should be continually treated such that they always comprise systemic overproduction of activated factor X. Thus, while the claimed products might be useful in stopping a bleeding episode in a hemophilia A patient once such an episode has started (i.e. “treating” the bleeding) it does not appear reasonable that the claimed products are to be continuously administered for the life of the patient such that excess bleeding is "prevented" from ever occurring.

5. Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bispecific antibodies which comprise a) full length VH and VL sequences for each specificity (i.e. a total of 4 sequences), b) one full length sequence (VH or VL) for anti-FIX specificity and one full length sequence (VH or VL) for anti-FX specificity, c) the 12 CDR sequences that when interspersed among appropriate framework sequences yield the desired specificities (i.e. 6 for FIX (CDRs 1-3, heavy and light), and 6 for FX) , or d) 6 CDRs for one specificity with a minimum of one full length sequence (VH or VL) for the other specificity, does not reasonably provide enablement for antibodies comprising partial structural information or partial sequence “functionally

equivalent thereto" other than that which has been previously specified. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has claimed bispecific antibodies that bind factor IX and factor X, and such an antibody must also have cofactor-like activity which enhances enzymatic activity. Structural information recited for such antibodies consists of either heavy chain CDR3 sequences alone (claim 5) or the 3 heavy chain CDR sequences without any sequence information for the light chain.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

It is also known in the art that very different VH chains (about 50% homologous) can combine with the same $V\kappa$ chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different $V\kappa$ sequences to produce antibodies with very similar properties. These results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (FUNDAMENTAL IMMUNOLOGY, William E. Paul, M.D. ed., 3d ed. 1993, page 242). It is also known that given one specified variable domain, either

heavy or light, that skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain (heavy or light) is used in the screening assay.

Since all CDRs contribute to binding, and binding can be disrupted in unpredictable ways due to mutations as small as a single point mutation, applicant's claimed genus of antibodies wherein a single CDR is the only structural information recited in the claims, does not reasonably appear to be enabled. The instant specification provides no data indicating that the heavy chain CDR3 peptide alone is sufficient for antigen binding, and using SEQ ID NO:40 of the instant invention as a example, the same sequence can be found in multiple other antibodies which differ in antigen specificity (see enclosed alignments). Thus it is clear that just the heavy chain CDR3 sequence is insufficient to confer antigen specificity upon the recited antibody. The required amount of recited sequence is even less since the recitation of "sequences functionally equivalent thereto" allows for mutations, which are known to unpredictably influence binding as per Rudikoff et al. Note that even a recitation of all 3 CDRs of a variable domain (either VH or VL) would also not allow a skilled artisan to make the instant claimed invention because a complete variable domain is required for use in screening assays that would identify suitable binding pairs that maintain antigen specificity.

Therefore, based upon the breadth of the claimed invention, the teachings of the art, and the lack of guidance and direction disclosed in the specification, a skilled artisan would be unable to make and use the full breadth of the claimed genus of antibodies without first performing additional, unpredictable research.

6. Claims 1-13, 15, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed a broad genus of bispecific antibodies which have the ability to functionally substitute for a cofactor of an enzyme. The independent claim does not recite the identity of the enzyme, substrate or cofactor, while dependent claims indicate that the enzyme bound by the bispecific antibody is factor IX, that the substrate bound by the bispecific antibody is factor X, and that the bispecific antibody serves as a cofactor because it increases the enzymatic activity of factor IX, similar to the role played by factor VIII in vivo. The specification also asserts other enzyme/substrate/cofactor groupings that could be bound by bispecific antibodies on pages 13 and 14 of the specification, although the working examples deal only with bispecific antibodies which bind factors IX and X. These examples indicate that antibodies were made that bound factors IX and X, that such antibodies were humanized by CDR grafting into human frameworks (page 42) and that the separate antibody specificities were made into a bispecific antibody structure using art recognized techniques (pages 31-33). Note that in addition to binding two distinct antigens, the claimed bispecific antibodies are also required to comprise the functional property of enhancing enzymatic activity in lieu of a cofactor (i.e. "functionally substituting for a cofactor"). The instant claims either recite no specific structure (such as claim 1) for the claimed genus or recite partial structures, such as CDR sequences by SEQ ID number (claims 5 and 6).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court stated: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, the independent claim is not limited to any specific enzyme/substrate/cofactor combination, and the claim requires the bispecific antibody to comprise the functional property of substituting for a cofactor. Such antibodies are not typical. For example, antibodies that bind FIX/FIXa and inhibit its coagulation activity have been described by many groups in the prior art (Bajaj et al., Bessos et al., Nilsson et al., and US patent 6,005,091) and thus it was surprising that the antibodies of Scheiflinger et al. (US patent 7,033,590, of record) increase the procoagulant activity of factor IX and display factor VIII-like activity. Thus it is clear that while antibody binding to antigen is necessary for cofactor activity, simple binding per se is not sufficient to supply cofactor activity. Thus the structure that is correlated with activity in the case of factor IX is the epitope of factor IX that when bound by an antibody increases its

enzymatic activity. Thus antibodies that bind this epitope can either be described by reciting the sequence of the epitope within the primary sequence of factor IX that is bound, or by reciting sufficient structural portions of the antibody which will ensure binding to the required epitope. The epitope within factor IX bound by the antibodies of the working examples does not appear to have been mapped or disclosed, but applicant has recited partial structural information for species within the claimed genus of antibodies. Specifically, dependent claim 5 recites the CDR3 sequence of the heavy chain alone, while dependent claim 6 recites the 3 CDRs of the heavy chain without any recitation concerning the light chain.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

It is also known in the art that very different VH chains (about 50% homologous) can combine with the same Vκ chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different VH sequences combine with different Vκ sequences to produce antibodies with very similar properties. These results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (FUNDAMENTAL IMMUNOLOGY, William E. Paul, M.D. ed., 3d ed. 1993, page 242). It is also known that given one specified variable domain, either

heavy or light, that skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain (heavy or light) is used in the screening assay.

Since all CDRs contribute to binding, and binding can be disrupted in unpredictable ways due to mutations as small as a single point mutation such mutations being encompassed by the breadth of the claims due to the recitation of "a complementarity-determining region functionally equivalent thereto", applicant's claimed genus of antibodies wherein a single CDR is the only structural information recited in the claims does not provide a reasonable correlation between structure and the function of increasing enzymatic activity. Note that the instant specification provides no data indicating that the heavy chain CDR3 peptide alone is sufficient for antigen binding or augmentation of enzymatic activity, and thus the structure represented by the CDR3 sequences is not correlated with the recited functional properties. Further, using SEQ ID NO:40 of the instant invention as an example, the same sequence can be found in multiple other antibodies which differ in antigen specificity (see enclosed alignments). Thus it is clear that just the structure of the heavy chain CDR3 is not correlated with the functional properties of antigen binding and cofactor activity. The required amount of recited sequence is even les since the recitation of "sequences functionally equivalent thereto" allows for mutations, which are known to unpredictably influence binding as per Rudikoff et al. Note that even a recitation of all 3 CDRs of the heavy chain, as is currently found in claim 6, also does not satisfy the need for a correlation between structure and function since there is no data that the 3 heavy chain CDR sequences by themselves, either with or without framework regions (i.e. free peptides of a complete variable domain) comprise the recited activity of substituting for a cofactor without the addition of an appropriate light chain variable domain. Thus the structures disclosed by the specification which are correlated with the activity of increasing factor IX activity and thus behaving as a factor VIII-like cofactor are the sequences of the variable domains of

the antibodies made in the working examples. Such structures are reasonably disclosed as either the complete sequence of both the heavy and light chain variable domains, or the sequences of the six CDRs (3 from the heavy chain and 3 from the light) which are found in said variable domains. Note that the specification does not provide a correlation of a structure with function for any enzyme/substrate/cofactor group excepting factor IX/X/VIII.

Therefore, it appears that applicant's claimed bispecific antibodies lack adequate written description because the breadth of the claimed genus is not supported by either a representative number of examples covering the breadth of the claimed subject matter or a disclosure of the epitope within an enzyme that when bound by an antibody gives rise to the functional property of increasing enzymatic activity. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of bispecific antibodies at the time the application was filed.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 15 provides for the use of an antibody, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claim 15 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-4 and 7-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheiflinger et al. (US Patent 7,033,590, of record) in view of Paulus (US Patent 4,444,878, of record).

Scheiflinger et al. disclose antibodies that bind factor IX and increase the procoagulant activity of factor IX (see entire document, particularly the abstract, column 2, and claims 1-22). These antibodies are disclosed as having FVIII cofactor-like activity, and were demonstrated to have this activity even in the presence of anti-FVIII inhibitory antibodies (see column 2 and examples 2-9, particularly example 7). The antibodies of Scheiflinger et al. are disclosed as being bispecific (see particularly lines 30-50 of column 7) and as being useful for treating multiple conditions associated with

excessive bleeding, such as factor VIII inhibitor patients (see particularly columns 2 and 9). The antibodies are also disclosed as being present in therapeutic compositions in various physical forms (column 7). Scheiflinger et al. further disclose that blood coagulation is an enzymatic cascade pathway, that factor IX activates factor X, and that the end result of this pathway is the formation of a stable blood clot made of fibrin (see particularly columns 1 and 2). Note that activated factor IX activates factor X, and thus factor X is a substrate of factor IX. These teachings differ from the claimed invention in that the other antigen recognized by the bispecific antibodies of Scheiflinger et al. is not disclosed as being factor X.

Paulus discloses that bispecific antibodies are to be used as scaffolding to bring together enzymes that belong to the same enzymatic pathway to enhance the efficiency of the reaction pathway (see entire document, particularly column 5 and figures 4 and 5).

Thus, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to make the bispecific antibodies of Scheiflinger et al. also target factor X since it was known that both enzymes operate in the same enzymatic pathway and since it was known that aggregating enzymes that belong to the same enzymatic pathway by way of bispecific antibodies increases the efficiency of the enzymatic pathway as disclosed by Paulus. A person of ordinary skill in the art would have a reasonable expectation of success in making such antibodies since methods of producing bispecific antibodies were known in the art at the time the invention was made as evidenced by the art cited by Scheiflinger et al. concerning the production of such molecules, the data presented by Paulus demonstrating that efficiency increases when enzymes that are part of the same pathway are joined by bispecific antibodies, and the demonstration by Scheiflinger et al. that their antibodies comprise FVIII-like cofactor activity.

13. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scheiflinger et al. (US Patent 7,033,590, of record) in view of Paulus (US Patent

4,444,878, of record) as applied to claims 1-4 and 7-13 above, and further in view of Zuk et al. (US Patent 4,208,479).

The teachings of Scheiflinger et al. and Paulus have been discussed supra. These teachings differ from the instant claimed invention in that their bispecific antibodies are not disclosed as part of a kit.

Zuk et al. teach that providing reagents, such as antibodies, in kits offer the advantages of substantial convenience and enhanced accuracy when performing methods involving said reagents (see entire document, particularly from line 20 of column 22 to line 27 of column 23).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to place the bispecific antibodies rendered obvious by the combined teachings of Scheiflinger et al. and Paulus into a kit. Motivation to do so comes from the teachings of Zuk et al. that providing reagents in kit form provides the advantages of increased convenience and accuracy when performing immunological methods, such as the methods of treating hemophilia and other bleeding disorders disclosed by Scheiflinger et al..

14. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scheiflinger et al. (US Patent 7,033,590, of record) in view of Paulus (US Patent 4,444,878, of record) and in view of Zuk et al. (US Patent 4,208,479) as applied to claims 1-4, 7-13, and 16 above, and further in view of Lollar et al. (US patent 5,744,446).

The inventions rendered obvious by the combined teachings of Scheiflinger et al., Paulus, and Zuk et al. have been discussed above and differ from the instant invention in that such kits are not disclosed as comprising factor VIII as an additional reagent.

Lollar et al. disclose recombinant factor VIII polypeptides and indicate that such polypeptides are to be used in methods of treating bleeding disorders such as

hemophilia (see entire document, particularly the abstract, lines 20-25 of column 4, from line 50 of column 26 to line 15 of column 29, and claims 1-20).

Therefore it would have been obvious to a person of ordinary skill in the art to combine bispecific antibodies and factor VIII together into a kit because both reagents alone are useful for treating bleeding disorders, such as hemophilia. The courts have determined that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…. [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See MPEP 2144.06.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-13, 15, 16, and 18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 17, 19, 22, 25, 28, 29, 36, and 38 of copending Application No. 11/910,836. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application anticipate the breadth of the instant claimed invention. Specifically, the independent claim of the copending application is limited to a bispecific antibody that binds both blood factor IX and X, whereas the independent claim of the instant application is a bispecific antibody that binds an enzyme and a substrate, with FIX and FX binding appearing as dependent limitations. Both applications also claim compositions and kits comprising such antibodies, including kits that further comprise FVIII.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

18. Claims 1-13, 15, 16, and 18 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 23-35, 37, and 38 of copending Application No. 10/575,905. Specifically, instant claims 1-4 and copending claims 23-26 are word for word identical. Further, as evidenced by the enclosed sequence alignments, the same biological sequences are disclosed and claimed in the two applications. Further dependent claims also are of the same scope and wording. This

is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

19. No claims are allowable.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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